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HEAD TO HEAD

Should we screen for cirrhosis?

Recent guidelines are right to recommend screening high risk patients for liver cirrhosis, say **Mark Hudson** and **Nick Sheron**. But **Ian Rowe** and **Gideon Hirschfield** worry about the lack of a suitable screening test

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Yes— Mark Hudson and Nick Sheron

Liver disease is the second leading cause of potential years of working life lost in England and Wales (72 684), after ischaemic heart disease (77 432). But although years lost from ischaemic heart disease have fallen by a factor of four since 1979, those from liver disease years have increased threefold and are still increasing.[1] The increase is in constrast to the trend in Mediterranean regions of Europe (France, Italy, Spain, Portugal, and Greece), which historically had the highest cirrhosis mortality but have seen significant declines. Reduction in alcohol consumption, hepatitis B vaccination and reduced hepatitis C transmission have contributed to this decrease.[2]

Liver disease will probably overtake heart disease to become the commonest cause of death in working age people in England and Wales in the next year or so. Only a third of patients admitted to hospital with liver disease will recover. There is no indication that things are improving, and there are at least two reasons for this.

Firstly, therapeutic options for the commonest causes of liver disease, alcohol and obesity, are limited. Secondly, liver disease develops without signs or symptoms, and many patients present with often fatal complications of late stage cirrhosis. Data presented in the Lancet commission report in 2014 indicated that 75% of 5000 patients admitted as an emergency for liver disease in Southampton had not been previously referred to a liver or gastroenterology clinic, suggesting that the liver disease had not been detected beforehand.[3]

Detection in primary care

Liver disease takes between 10 and 50 years to progress through fibrosis to cirrhosis, portal hypertension, liver failure, and liver cancer. It ought to be possible to detect patients with cirrhosis in primary care, but there diagnosis relies on tests for the enzyme alanine transaminase (ALT), and ALT concentrations are unrelated to stage of liver fibrosis; a recent systematic review found that 90% of patients with cirrhosis would not have been identified using standard liver tests.[4]

The answer is to go upstream. A 30 year upward trend in mortality from liver disease in the UK was reversed by the 2008 budget, which increased alcohol duty; however, the policy was abolished in 2013, at a cost of £3.5bn in lost duty, and since then liver deaths have been increasing again.[5] Similarly, the solution for clinical hepatology is to go upstream; the technologies to identify early liver disease exist and are supported by the National Institute for Health and Care Excellence (NICE).

NICE guidelines

Recent guidelines on cirrhosis from NICE recommend that men and women drinking alcohol at potentially harmful levels—more than 50 and 35 units a week, respectively—be offered transient elastography (fibroscan) to exclude cirrhosis.[6] This equates to about 2.25 million people in England and Wales. Reports suggest elastography is an efficient technique to exclude the diagnosis of cirrhosis whatever the cause. With a cut-off value of 14.6 kPa, chosen to obtain a 95% specificity, positive and negative predictive values for diagnosing cirrhosis are 74% and 96% respectively.[7]

Currently few GPs have access to this test so change is not going to happen overnight. However, because the lifetime cost of treating liver disease is between £50 000 and £120 000,[8] this approach is likely to be cost effective.

One important question remains: if we detect patients with cirrhosis earlier, can we prevent progression of the disease? There are already highly effective treatments for viral hepatitis and autoimmune liver disease, and numerous compounds are in advanced clinical trials for non-alcoholic fatty liver disease.[9] About 40-50% of patients with alcohol related liver disease will stop drinking after admission with cirrhosis,[10] and evidence from

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a feasibility study shows that a community diagnosis also reduces hazardous drinking.[11]

We will need properly controlled trials, and these studies are in preparation. However, the burden of liver disease is such that doctors cannot simply sit in their ivory towers waiting for patients with liver disease to come and find them.\

No— Ian Rowe and Gideon Hirschfield

Despite recent recommendations from NICE,[6 12] insufficient evidence supports a screening programme for cirrhosis.

Histologically definable cirrhosis is the culmination of many liver injuries, some prevalent (alcohol, non-alcoholic fatty liver, and viral) and others rare (genetic, autoimmune). Regardless of cause, cirrhosis carries an increased risk of complications—namely, liver failure, primary liver cancer (hepatocellular carcinoma), and ultimately death.

As physicians in busy liver units we see complications of liver disease every day, so conceptually, cirrhosis seems an attractive target for screening to prevent an array of costly personal and societal events. The rising burden of liver disease in the UK, with a 400% rise in death rates since 1970, sweetens this appeal.[3] But conceptual simplicity must not be confused with validated justification.

For a successful screening programme the test used must be simple, cheap, and, most importantly, accurate. Early identification of disease is of benefit to patients only if there are effective surveillance strategies or treatments that can be implemented as a result. Any screening intervention must also be cost effective.

Evidence is lacking

A focus on the largest group at risk, the three million people in the UK estimated to be drinking alcohol hazardously,[13] highlights where evidence to support screening is lacking.

The test proposed to screen for cirrhosis—transient elastography—is not widely available and would require huge up-front investment to establish it in community settings. It has also been shown to perform poorly in people suspected to have alcohol related liver disease, with a false positive rate of 29%.[14] Using this test to screen all hazardous drinkers would therefore lead to many people being incorrectly labelled as having cirrhosis.

For example, if one million hazardous drinkers were screened and the true prevalence of cirrhosis among them is 10%, about 260 000 people would be falsely labelled as having cirrhosis—more than double the true number.

These people would subsequently be subjected to unnecessary surveillance interventions—including regular ultrasonography for the early diagnosis of liver cancer and upper gastrointestinal endoscopy for the detection of large oesophageal varices—without any prospect of benefit and the risk of complications. In addition, concerns raised about the complications of cirrhosis, including the development of liver cancer, may cause psychosocial harms.[15]

The most important action for a patient at risk of, or with, alcohol related liver disease is to reduce their alcohol consumption. This is recommended regardless of the result of any screening test for cirrhosis because it not only prevents progression of liver disease but protects the person from other harms related to hazardous alcohol consumption.

Existing brief alcohol interventions have been proved effective in reducing alcohol consumption.[16 17] Whether they are enhanced by a screening test for cirrhosis is unknown. Without this evidence, it is more rational to identify people at risk of cirrhosis and implement interventions known to improve their health.

Surveillance interventions for patients with cirrhosis are associated with an uncertain benefit in terms of reducing mortality from liver disease. Surveillance for the development of liver cancer in particular is controversial since it is not supported by randomised controlled trials.[18 19]

Opportunity costs

Finally, a screening programme for cirrhosis could worsen population health when healthcare resources are limited. Screening for cirrhosis in people who drink alcohol hazardously is probably not cost effective at the £20 000 per quality adjusted life year (QALY) threshold.[6] The true cost effectiveness would likely be even less because the modelling included unrealistically positive estimates of long term abstinence rates after screening.[20]

At that level of cost effectiveness, and given the resource constraints in the NHS, implementation of screening for cirrhosis would inevitably lead to disinvestment in other, more effective interventions, risking the overall health of the population.[21]

Treating the most common liver diseases requires a risk factor based approach—using brief interventions to reduce alcohol consumption and addressing obesity and metabolic risk factors in people with non-alcoholic fatty liver disease—rather than a specific diagnosis of cirrhosis.

Resources should be targeted at managing these risk factors as well as investing in well designed trials that evaluate the clinical and cost effectiveness of screening strategies employing more widely available and accurate blood test based tools,[22] starting in people at risk of alcohol related liver disease. Currently, though, the evidence does not support screening.

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